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CHEMICALLY-MODIFIED CELLULOSIC POLYMERS

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ABSTRACT

Chemically-modified celluloses are among the most commonly and widely used polymers in the food, cosmetic, and pharmaceutical industries today. Several products with widely different physico-chemical properties are currently commercially available. Some of the major applications of these include their use as: i) tableting aids (binders, fillers, disintegrants); ii) viscosity imparting agents in the preparation of semi-solid, solution, and suspension formulations (e.g, creams, gels, lotions, suspensions, shampoos, hair conditioners, food products, etc.); iii) taste and odor masking agents; iv) coating materials for tablets and other dosage forms; v) carriers for cosmetic and topical formulations; and vi) carriers including controlled- and/or sustained-release carriers for veterinary, agricultural, and pharmaceutical preparations. In this article, a general overview of various chemically-modified cellulosic products used in pharmaceutics, is presented.

INTRODUCTION

Cellulose, the starting polymer source for all cellulose derivatives, has been the primary component of man's diet since the

beginning of human history. It is the most abundant natural polymeric raw material. All forms of plant life contain cellulose. Based on its nearly ubiquitous distribution in nature, and humankind's long exposure to cellulose, cellulose and its derivatives are generally recognized as the safest and most acceptable polymer class for use in food and pharmaceutical products. As supplied in nature, it is free of chemical contaminants (e.g., residual monomers, initiators, or catalysts) commonly present in the synthetic polymer sources. The cotton fiber is the purest source of cellulose. However, a large portion of cellulose for industrial use is obtained from wood sources. The composition of cellulose in wood varies from one wood source to another. In general, wood contains cellulose between 40-55%, on a dry weight basis. The other major components of wood are lignin (15-35%) and hemicelluloses* (25-40%)[1].

Structurally, cellulose consists of repeating units of anhydro β-D glucopyranose units, linked together by β-1,4-glycosidic bonds (Figure 1). The CH_2OH, OH, and the glycosidic bonds are all equatorial with respect to the planes of the pyranose rings. The reducing end unit of the cellulose chain contains a hemiacetal group (on C-1), and exhibits chemical properties similar to those of the glucose. The non-reducing end unit contains an additional secondary alcohol group (on C-4) and is useful in the determination of the number-average degree of polymerization (DP). Because of it's high degree of polymerization, the general chemical and physical properties of cellulose are determined by the intermediate units.

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*Hemicelluloses are not forms of cellulose. They contain several sugar units and exhibit a considerable degree of branching. The most abundant sugar units are 1,4-linked β-D-xylopyranose (some bearing short side chains of 1,3-linked α-L-arabinofuranose or esterified 1,2-linked α-D-glucuronic acid) and 1,4-β-D-glucomannans with or without 1,6-linked α-D-galactopyranose units as side chains. The glucose and mannose units are also present but their distributions are random.

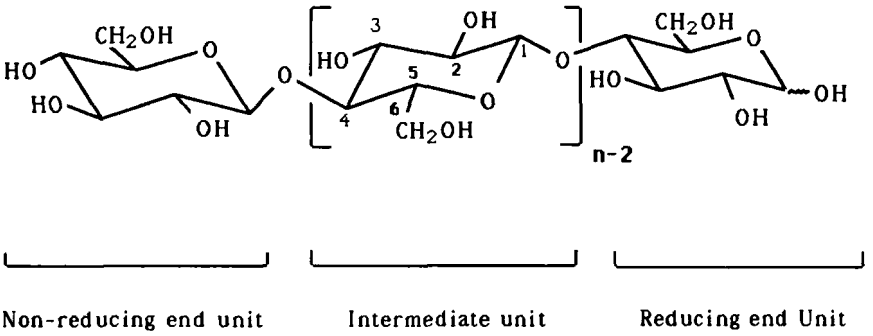


FIGURE 1

Structure of Cellulose

The stereochemistry of cellulose is such that two types of intra-chain hydrogen bonding exist. These include bondings between the C-2 hydroxyl hydrogen and the pyranose ring oxygen atom on one side of each pyranose residue, and between the C-3 hydroxyl hydrogen and the C-6 hydroxyl oxygen atoms on the other side[2]. As a result of these bondings, the β-D glucopyranose ring assumes a ^{4}C-chair configuration. When fully extended, the cellulose chain appears as a flat ribbon, with hydroxyl groups protruding laterally and hydrogen atoms lying above and below the pyranose ring plane. In the native form, cellulose chains are further linked laterally by the inter-chain hydrogen bonds, occurring between the C-6 hydroxyl hydrogen on one chain and the C-3 hydroxyl oxygen atom on the other[2]. These laterally bonded cellulose chains in turn stack together, through weak van der Waals forces, to give a three-dimensional layered structure[2,3]. The inter- and intra-chain hydrogen bonding network of cellulose is reproduced in Figure 2.

The molecular alignments of the cellulose polymer chains in the cellulose fibril are best described by the fringe-micellar model and the chain-fold model (Figure 3)[4]. According to the fringe-micellar model, cellulose chains are fully extended and arranged in an array, parallel to the axis of the fibril, whereas in the folding-chain model, cellulose chains fold back and forth, within the [101] plane of the crystalline

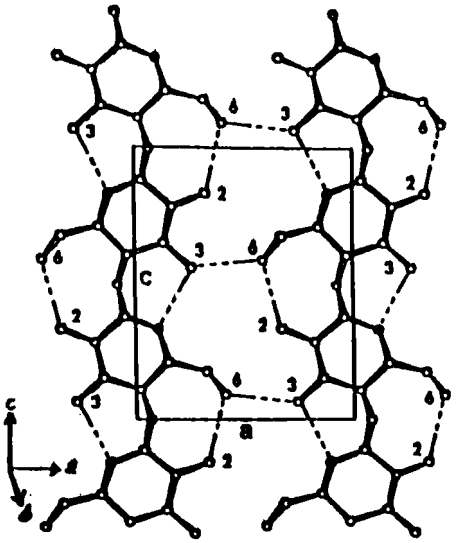


FIGURE 2

Inter-and Intra-chain Hydrogen Bonding Network[2a]

lattices, to give a sheet-like platelet structure. The transverse dimension measures about 40 A and the length of the crystalline region averages about 500 A for native cellulose and about 150 A for regenerated cellulose[4]. As shown in the Figure, the crystalline regions along the fibril axis are interrupted by the less ordered regions, called amorphous regions. These regions can result from damage during the dispersion processing of wood pulp or other cellulose raw materials, from different chain order bondings (e.g., occurrence of β-1,6 linkage[5] instead of the regular β-1,4 glycosidic bond), as a result of natural surface imperfections, and from strained or twisted regions of the molecular crystallite strands. These may range from 10% to 30%, by weight, of the fiber[4]. These amorphous regions lack hydrogen bonding, and therefore constitute the major centers of chemical reactivity in a chemical reaction.

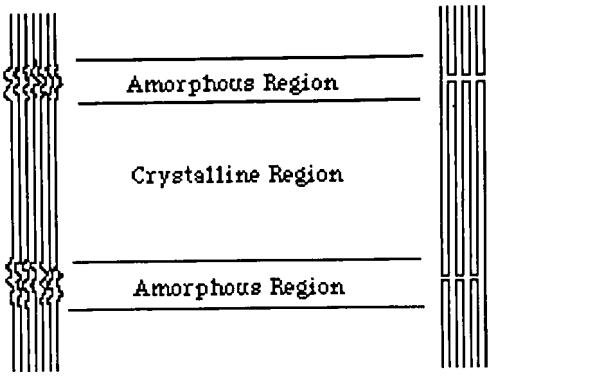


FIGURE 3

Molecular Alignments of Cellulose Chains

Cellulose, owing to its high crystallinity and cohesive density, is insoluble in water. It does, however, show some affinity to water. The amount of moisture that can be adsorbed depends on the degree of crystallinity of the cellulose source. The higher the degree of crystallinity, the lower the number of accessible hydroxyl groups for binding with water molecules, and hence, the lower the water adsorption characteristics of the material. Zeronian et al.[6] reported that cotton cellulose regains about 6.38% of water when stored at 59% relative humidity and at 21°C, whereas under identical conditions the amorphous cellulose adsorbs about 18.17% moisture.

The chemical reactions of cellulose are complex in nature. This is because: i) cellulose is insoluble in most reaction media, and nearly all reactions are performed under heterogeneous conditions; and ii) cellulose has a complex physical structure (i.e., the presence of widely and irregularly spaced crystalline and amorphous regions with complex microstructural features) that causes cellulose microfibrils to exhibit widely different accessibilities to the same reagent. Higher crystall-

inity means higher degrees of order of arrangement and hydrogen bonding between cellulose chain molecules, whereas higher accessibility represents an increased lack of order of molecular arrangement and hydrogen bonding. Thus, the chemical reactivity of cellulose is greatly dependent on the degree of crystallinity; the lower the degree of crystallinity (and the higher the number of accessible regions), the higher the chemical activity. Other factors that may significantly influence cellulose reactions are the nature (e.g., molecular size and polarity) of the reagent and the swelling power of the reaction media.

The principal reaction sites in cellulose are: 1) three hydroxyl groups (on positions C-2, C-3, and C-6) occurring on opposite sides of the chain in each repeating glucopyranose unit; and ii) the glycosidic linkage. The former exhibit chemistry (e.g., oxidation, etherification, and esterfication reactions) similar to that of alcohols, whereas the latter is highly prone to hydrolysis and alcoholysis. The acidity and tendency for dissociation of the hydroxyl groups depend on the neighboring substituents, and are widely accepted to follow the order 2-OH > 3-OH > 6-OH[7]. The relative reactivity order, however, may vary from one reaction to another, depending on the reaction conditions[8]. In reactions in which the ionization of hydroxyl groups is not a rate-limiting step (e.g., esterification), the OH-6, being primary in nature and being the least sterically hindered of the three hydroxyl groups present, is usually the preferred site of attack.

CELLULOSE PRODUCTS

The various chemically-modified cellulose products used in food, cosmetic, pharmaceutical, medical and related applications can be grouped into four classes, based on their methods of preparation (Figure 4). These are: hydrocelluloses, cellulose esters, cellulose ethers, and oxycelluloses. The cotton linters or cellulose pulp are usually used as a starting polymer source.

HYDROCELLULOSES. These are white, water-insoluble solid residues prepared by partial heterogeneous or homogeneous hydrolysis of

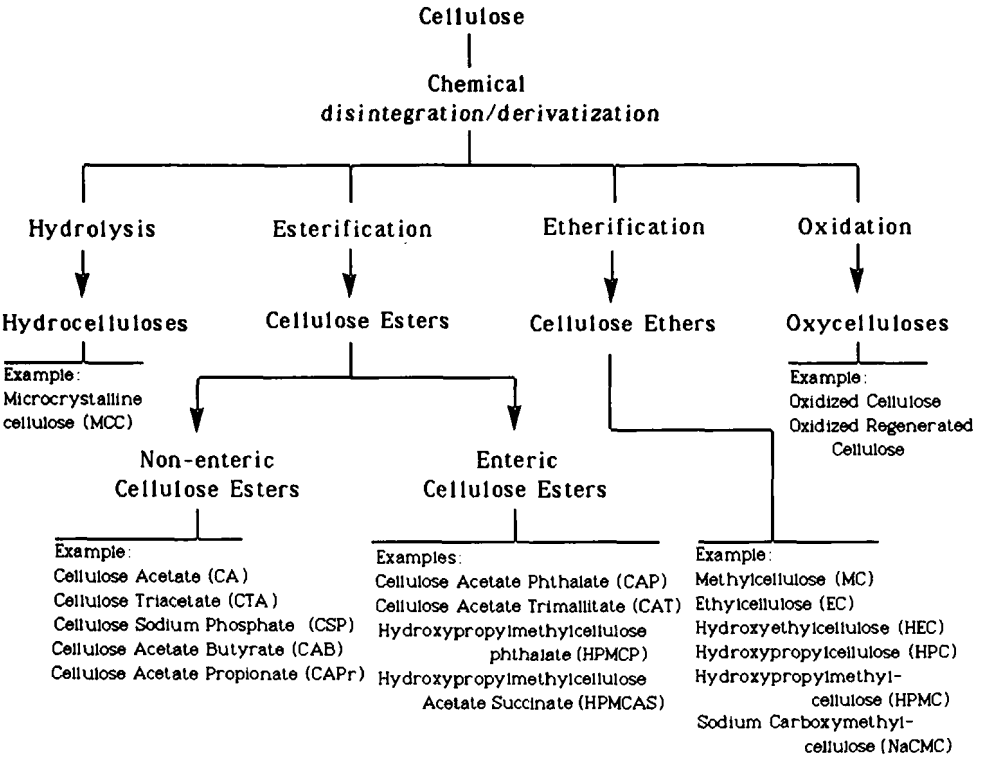


FIGURE 4

Chemically-Modified Cellulose Products

cellulose with acids (e.g., hydrochloric[9], sulfuric[9a,10], phosphoric[9a,11], hydrofluoric[12], formic[12a] and trifluoroacetic[13] acid and a mixture of hydrochloric acid and sulfuric or phosphoric acid[14]). In dilute acid conditions, an initial rapid hydrolysis of accessible glycosidic linkages, followed by a slow reaction that causes dissolution of the soluble fragments from the ends of the hydrolyzed cellulose chains[15], occur. Since no further reduction in the DP of the product occurs during the second step of the hydrolysis, the products are called level-off DP hydrocelluloses. The hydrolysis mechanism is widely believed to involve an initial, rapid protonation of the glycosidic oxygen atom, followed by a charge-transfer step (to C-1) producing a carbonium ion

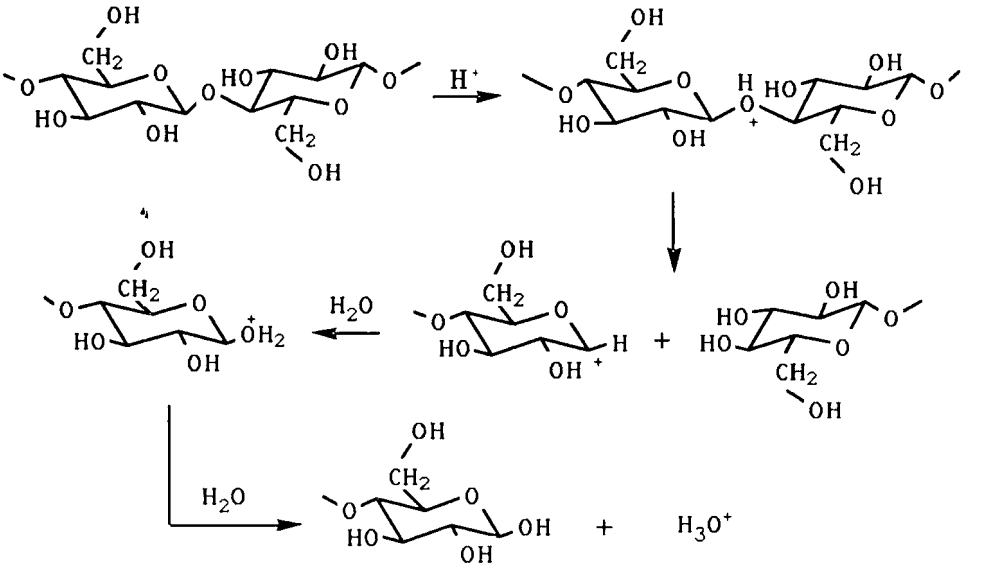


FIGURE 5

Acid-Catalyzed Hydrolysis of Cellulose

and cleavage of the glycosidic bond. The carbonium ion subsequently reacts with water to give the free cellulose residue and the hydroxonium ion[16] (Figure 5).

The degree of hydrolysis depends on the crystallinity of the initial starting cellulose material[4,9c,16a]. Battista et al.[9c] reported that the level-off DP of hydrocelluloses prepared from native fibers with 2.5N hydrochloric acid ranges between 200 and 300, whereas of those derived from the regenerated cellulose lies in the range between 15 to 60 and from alkali swollen natural forms of cellulose in the range between 60-125.

In concentrated acids, the hydrolysis of cellulose occurs rapidly and at moderate temperatures[16a]. The reaction involves an initial decrystallization step, causing swelling or dissolution of cellulose in the acid, followed by hydrolysis. The hydrolysis mechanism is the same as

shown in Figure 5. The products is isolated by diluting the reaction mixture with water or an appropriate water-miscible organic solvent. The DP and the degree of crystallinity of the product depends on the nature of the acid and its concentration, the reaction temperature, and the reaction time, used.

The first use of hydrocelluloses in cosmetic and pharmaceutical applications was reported by Battista[17] in 1964. The major application, however, is in the manufacture of microcrystalline cellulose (MCC). The MCC is the most commonly and widely used direct compression excipient in the solid dosage form design[9c,18]. The general manufacturing process of MCC involves further disintegration of the level-off DP hydrocelluloses in water to a colloidal gel which is then converted into a free flowing powder[19]. The high degree of crystallinity of the MCC powder renders good plastic deformation properties to particles on compression. The non-fibrous nature, plus the free flowing properties and the high surface area, make MCC the best dry binder available for tablets[20]. It also functions as a disintegrant and a lubricant in tablet manufacturing.

Commercially, MCC is available from the FMC Corporation under the trade name Avicel® PH (grades, average particle size, maximum percent moisture content: PH-101, 50μ, 5.0%; PH-102, 100μ, 5.0%; PH-103, 50μ, 3.0%; PH-105, 20μ, 5.0%; PH-112, 100μ, 1.5%; and PH-200, 200μ, 5.0%) and as EMCOCEL® from Edward Mendell, Inc. Avicel® is also available in water dispersible forms. These are designated as Avicel® RC and CL grades, Gelstar® cellulose gel, and MicroQuick WC-595. Both Avicel® RC and CL grades and the Gelstar® cellulose gel contain sodium carboxymethylcellulose (NaCMC), in addition to MCC, to aid dispersion and to serve as a protective colloid, whereas the MicroQuick WC-595 is a coprocessed blend of sweet whey, MCC, and NaCMC. MicroQuick WC-595 is designed for use in food systems that do not have adequate shear to achieve full dispersion. The compositions and pertinent physical properties of Avicel® RC and CL and Gelstar® grades are listed in Table 1.

TABLE 1

The Colloidal Grades of MCC[a]

	Avicel® (MCC + NaCMC)				
	RC-501	RC-581	RC-591	CL-611	Gelstar®
Process	Bulk dried	Bulk dried	Spray dried	Spray dried	Coprocessed
% NaCMC	7.1-11.9	8.3-13.8	9-15	11.3-18.8	12.0-20.0
Particle size (%), NMT					
+60 mesh	0.1	0.1	0.1	0.1	0.1
+200 mesh	40	35			45
+325 mesh			60	65	
Initial Viscosity, (cps)	72-168 at 2.1% disp.	50-168 at 1.2% disp.	39-175 at 1.2% disp.	50-151 at 2.6% disp	35-135 at 1.2% disp

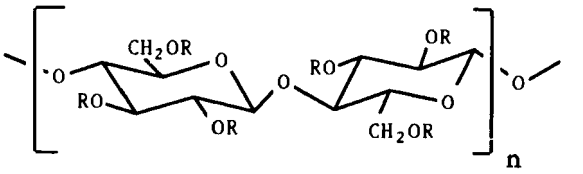
a. taken from Avicel® application bulletins C-87 and G-92.

Other Avicel® brand of cellulose gel available from FMC for use in food systems, as stabilizers and to control rheological properties, are Avicel® RCN-10, RCN-15, and RCN-30. Both RCN-10 and RCN-15 are a coprocessed mixture of MCC and guar gum, whereas RCN-30 contains MCC, xanthum gum and maltodextrin (FMC Data Sheet 5/10#9) .

Recently Wei and Banker[21a] have developed a new method to prepare low crystallinity hydrocellulose products. Depending on the procedure used, the low crystallinity cellulose product can be isolated as a powder or converted into a bead form or into an aqueous colloidal dispersion. The bead form functions as a disintegrant, whereas the powder form serves as a binder[21a]. The aqueous colloidal dispersion of the product can be used as a drug carrier and/or bodying agent in the preparation of topical formulations[21b]. The powder and the bead forms show much superior binder and disintegration properties, respectively, compared to materials currently commercially available [21a].

CELLULOSE ESTERS. These can be prepared by treating cellulose with acids (inorganic or organic acids), acid-anhydride mixtures, or acid chlorides, with or without the presence of a catalyst, under controlled conditions[22]. The catalysts commonly used are sulfuric acid, zinc chloride, phosphorus pentaoxide, and hydrogen chloride (gas). Generally, the reaction is allowed to proceed to substitute all three hydroxyl groups. The fully substituted triester derivative is then hydrolyzed to the desired level of substitution. The mixed acid esters are produced by treating cellulose first with one acid, and then, at an appropriate time, the other acid is added. By controlling the weight ratios of the two acids, products with different degrees of substitution (DS) (of each substituent) can be prepared[22]. The physicochemical properties (e.g., solubility, melting point, and glass transition temperature) of cellulose esters depend on both the nature of the substituent, and the degree and uniformity of substitution.

ENTERIC CELLULOSE ESTERS. These refer to polymers that remain insoluble in low acidic media, but dissolve in mild acidic to neutral aqueous solutions. Oral solid dosage forms coated with such polymers are intended to remain intact in the stomach, but to rapidly dissolve and release the active ingredient(s) in the upper intestine. Thus, enteric coatings in pharmaceutics are used to: i) deliver drugs that act locally in the intestine and require a high concentration at that site of effectiveness (e.g., some anthelmintics); ii) to protect a drug from destruction due to gastric media (e.g., enzymes, low pH environment); iii) prevent nausea, due the irritation of the gastric mucosa, or bleeding in the stomach; and iv) to target drug release at a particular region of the intestine for enhanced absorption. The various factors that influence the dissolution of enteric coatings are: i) the pKa of the polymer; ii) the total free carboxylic content; iii) the nature of the core material - (acidic core materials may produce a lower pH aqueous environment, relative to that of the bulk, on the coating layer and thus delaying the dissolution of the coating); iv) the ionic strength of the dissolution media; v) coating thickness; and vi) the presence or absence of plasticizers and other non-enteric components in the coating layer[31].



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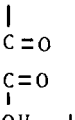
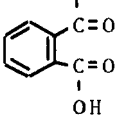
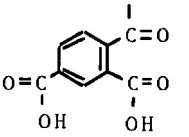
CA or CTA: -H or -CCH_3

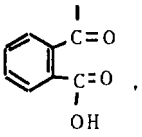
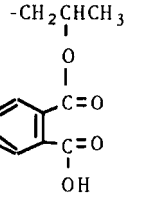
CSP: -H or -P(=O)(ONa)-ONa

CAPr: -H, -CCH_3, or -CCH_2CH_3

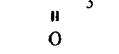
CAM: -H, -CCH_3, or 

CAP: -H, -CCH_3, or 

CAT: -H, -CCH_3, or 

HPMCP: -H, -CH_3, -CH_2CHCH_3,  or 

HMPCAS: -H, -CH_3, -CH_2CHCH_3, -CCH_3, -CCH_2CH_2COH, -CH_2CHCH_3, or



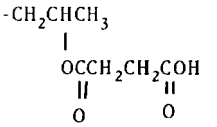


FIGURE 6

Structures of Cellulose Esters

The cellulosic enteric polymers include: cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), cellulose acetate maleate (CAM), hydroxypropylmethylcellulose phthalate (HPMCP), and hydroxypropylmethylcellulose acetate succinate (HPMCAS). The structures of these polymers are shown in Figure 6. Currently, only CAP[23] and HPMCP[24] are listed in the USP/NF.

A free flowing powder of CAP containing 35% phthalyl and 24% acetyl contents and 0.5% phthalic acid as a free (residual) acid is available from Eastman[25]. CAP is soluble in aqueous solutions of pH 6.2 and higher. A water-dispersible form of CAP is marketed by FMC as Aquateric®. It contains 63-70% CAP. Other components present are Pluronic F68 (a block copolymer of ethylene oxide and propylene oxide), Myvacet 9-40 (distilled acetylated monoglycerides), and Polysorbate 60 (polyoxyethylene (20) sorbitan monostearate)[26].

CAT is manufactured and marketed by Eastman. The trimellityl and acetyl contents and the free trimellitylic acid present in the product are 29%, 22%, and 0.5%, respectively. It dissolves in buffer solutions of pH 5.2 and higher[25].

CAM is the least studied of these polymers to date, and is not commercially available at this time. It is prepared by treating cellulose acetate with maleic anhydride and anhydrous sodium acetate at 95°C[27]. Murthy et al.[27] reported that sodium bicarbonate tablets coated with CAM exhibited satisfactory core-to-coat adhesion, acid-resistance, and no drug loss or coat disintegration in gastric media. In simulated intestinal juice, the tablets disintegrated slowly compared to tablets coated with CAP.

HPMCP is prepared by reacting hydroxypropyl methylcellulose with phthalic anhydride[28]. Although several grades of HPMCP are commercially available, only two grades of HPMCP are recognized in the USP/NF as substitution types 220824 and 200734, and are currently accepted for use in humans[24]. These are marketed under the trade names HP-50 and HP-55 by Shin-Etsu Chemical Co.[29] and HPMCP-50 and

HPMCP-55 by Eastman Chemical Co.[25] The HPMCP-50 and HP-50 dissolve at a pH of 4.8 and 5.0, whereas HPMCP-55 and HP-55 are soluble at pH 5.2 and 5.5, respectively.

HPMCAS is available in three grades, AS-LG, AS-MG, and AS-HG (or AS-LF, AS-MF, and AS-HF), from Shin-Etsu[30]. The letters G and F correspond to granule and fine powder forms of the product. The LG, MG, and HG grades are organic solvent soluble, whereas LF, MF, and HF are for making aqueous dispersions. The LG and LF grades of HPMCAS dissolve at a pH 5, MG and MF grades at 5.5, and the HG and HF grades at pH > 5.5.

In addition to their pH dependent solubility profiles in aqueous solutions, all these acid functionalized cellulose polymers (CAP, CAT, HPMCP, and HMPCAS) show solubility in a number of mixed organic solvent systems (e.g., acetone:water, acetone:methanol or ethanol, acetone: methylene chloride, ethyl acetate:ethanol or methanol, and methylene chloride: ethanol or methanol)[25,29]. The viscosity of the resulting solution depends not only on polymer concentration, but also on the solvent systems and the ratio of solvents used.

The coating solutions of these polymers can be prepared by dissolving polymer in an appropriate organic solvent or in a dilute aqueous solution of a base. An appropriate plasticizer is added to the solution to obtained the desired physical/mechanical properties of the coatings/films. Some very effective plasticizers that can be used are diethyl phthalate, glyceryl triacetate or triacetin, tributyl citrate, tributyrin, butyl phthalyl butyl glycolate, and glycerin. A comprehensive review of the enteric performance of these and various other cellulosic and non-cellulosic enteric polymers is presented in a book chapter by Agyilirah and Banker[31], and a comparison of rheological and enteric properties of organic and neutralized aqueous solutions of CAP, CAT, and HPMCP *(vide-infra)* and a latex CAP system are in a recent article by Chang[32].

NON-ENTERIC CELLULOSE ESTERS. These include polymers that do not show pH-dependent solubility profiles in water. Polymers belonging to

TABLE 2

Physicochemical Properties of Cellulose Acetates.

Grade	Acetyl/hydroxyl content (W%)	M_n (X1000)	DS	m.p. (°C)	T_g (°C)	Manufacturer
CA-435-75S	43.5/0.9	103	2.9	204-99	-	Eastman[34b]
CA-394-60S	39.5/4.0	60	2.45	240-60	186	"
CA-398-3	39.8/3.5	30	2.45	230-50	180	"
CA-398-6	39.8/3.5	35	2.45	230-50	182	"
CA-398-10	39.8/3.5	40	2.45	230-50	185	"
CA-398-30	39.7/3.5	50	2.45	230-50	189	"
CA-320-5	32.0/9.0	63.5	2.1	232-54	209	FMC[34a]
CA-398-10	39.8/3.4	58.5	2.7	212-50	191	"
CA-435-75S	43.7/0.9	160	2.9	286-306	179	"

this class include: cellulose diacetate (CA; commonly referred to as cellulose acetate), cellulose triacetate (CTA), cellulose sodium phosphate (CSP), cellulose acetate butyrate (CAB), and cellulose acetate propionate (CAPr). The structures of these are shown in Figure 6.

Of these, only CA and CSP are currently described in the USP/NF. The acetyl content in the cellulose diacetate[33a] and triacetate[33a] should not be less than 29.0 and not more than 44.8% and the amount of the bound phosphate in the cellulose sodium phosphate[33b] should be between 31% and 36%.

Cellulose acetates are prepared by treating cellulose with a mixture of acetic acid and acetic anhydride in the presence of sulfuric acid as a catalyst[22]. The reaction is generally allowed to proceed to substitute all three hydroxyl groups. The fully substituted triester derivative is then hydrolyzed to give the desired level of substitution. Cellulose phosphate is produced by reacting cellulose with phosphoric

acid in molten urea or with a mixture of phosphoric acid and phosphorus pentaoxide in alcohol, followed by isolation as a sodium salt[22].

The various grades of cellulose acetates commercially available, and their DS values, molecular weights, melting points, and glass transition temperatures (T_g), are listed in Table 2.

The solubility of cellulose acetates in organic solvents varies with the level of substitution as well as its distribution in the product[22]. As the acetyl content in the product increases, the choice of solvent systems to dissolve the polymer becomes limited. For example, cellulose diacetates are soluble in cyclohexane, methylketones, chlorinated solvents , acetone, and acetone-alcohol mixtures, whereas cellulose triacetate can be best dissolved in chlorinated solvents containing an appropriate amount of a low molecular weight alcohol[22,34]. The moisture permeability of cellulose acetate films increases with a decrease in the acetyl content[34a].

The CAB and CAPr are also available in various viscosity (molecular weight) grades[34b]. The applications of these in microencapsulation and drug-loaded microsphere preparations, by precipitation method using a solvent/non-solvent mixture or by evaporation of a volatile solvent from a non-aqueous or an aqueous emulsion, have been extensively investigated[34b,35,36].

Both cellulose diacetate and triacetate are good film-forming agents, and have been used in a variety of pharmaceutical applications. Several studies have been reported describing the use of cellulose diacetate in the preparation of sustained-release solid dosage forms[34,37]. Crome et al. reported the use of a cellulose acetate coated charcoal hemoperfusion system in the treatment of severe hypnotic drug intoxication[38]. The applications of cellulose triacetate include its use in kidney dialysis membranes[39] and in the preparation of transdermal patches[40]. Cellulose triacetate-based ultramicroporous (Poroplastic®) membranes have been designed to give a first-order

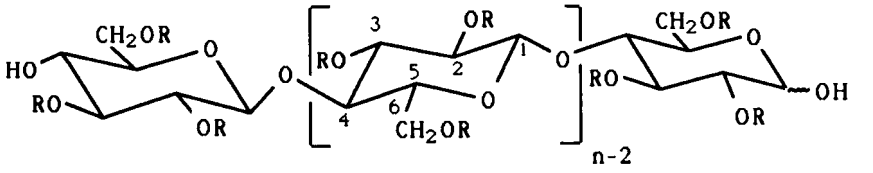
release monolithic, zero-order release distinct reservoir , and zero-order monolithic transdermal patch systems[40].

Cellulose sodium phosphate is currently marketed as a prescription drug under the trade name Calcibind® (Mission Pharmacal) for the treatment of hypercalciuria. The inorganic phosphate content and the sodium content in the product are approximately 34% and 11%, respectively[41]. It is given orally. According to one study[42], cellulose sodium phosphate when given at a 15 grams daily dose is more potent than the neutral sodium phosphate in decreasing calciuria. It promotes an increase in feces calcium and a decrease in urine calcium, with only a moderate change in the urinary phosphate amount. No increase in the oxalate amount has been noted when patients with stones were treated with cellulose sodium phosphate[42]. Cellulose sodium phosphate also binds intestinal calcium and, therefore, is useful in reducing calcium uptake from a high-protein diet[43].

CELLULOSE ETHERS. The most common method to prepare cellulose ethers is by nucleophilic substitution. Typically, the cellulose is first converted into an alkali cellulose, followed by a reaction with an appropriate nucleophilic agent, under controlled conditions[44]. The alkali cellulose can be prepared by treating cellulose with a base[45]. Sodium hydroxide is usually used, but other alkali metal hydroxides can also be used. The alkali treatment also causes swelling and decrystallization of cellulose[46], and consequently increases the number of accessible regions in the cellulose.

The various cellulose ethers currently described in the USP/NF are: methylcellulose (MC)[47a], ethylcellulose (EC)[47b], hydroxyethylcellulose (HEC)[47c], hydroxypropylcellulose (HPC)[47d], hydroxypropylmethylcellulose (HPMC)[47e], sodium carboxymethylcellulose (NaCMC)[47f], and calcium carboxymethylcellulose (CaCMC)[47g]. The structures of these are shown in Figure 7.

MC and EC are examples of alkyl cellulose ethers. These are prepared by treating alkali cellulose with methyl halide[46,48] and ethyl



Methylcellulose (MC):	R = -H, $-CH_3$
Ethylcellulose (EC):	R = -H, $-C_2H_5$
Hydroxyethylcellulose (HEC):	R = -H, CH_2CH_2OH, $-CH_2CH_2OCH_2CH_2OH$
Hydroxypropylcellulose (HPC):	R = -H, $-CH_2CH(OH)CH_3$
Hydroxypropylmethylcellulose (HPMC):	R = -H, CH_3, $-CH_2CH(OH)CH_3$
Sodiumcarboxymethylcellulose (NaCMC):	R = -H, $-CH_2COONa$

FIGURE 7

Structures of Cellulose Ethers

halide[46,49], respectively. HEC and HPC are hydroxyalkyl ether derivatives of cellulose, whereas HPMC is a mixed alkyl hydroxyalkyl cellulose ether. The HEC and HPC are prepared from reactions (of alkali cellulose) with ethylene oxide[46,50] and propylene oxide[46,51], respectively, whereas HPMC is prepared by reacting alkali cellulose with a mixture of methyl chloride and propylene oxide[46,48]. NaCMC is prepared from a reaction between alkali cellulose and sodium monochloroacetate[46,52].

Except EC, all the other cellulose ethers (MC, HEC, HPC, HPMC, and NaCMC) are water soluble. The hydration rates of these polymers depend on the nature of the substituent present and the degree of substitution (or moles of substituent, MS). The pH and temperature of the dissolution media and the particle size of the product may also influence the hydration rates. In general, the hydrophillicity of

cellulose ethers, within each class, decreases with an increase in the alkyl chain length. For example, HPC is more slowly hydrated than HEC. It precipitates from its solution at 40-45°C, whereas HEC remains in solution even at boiling temperature[44]. Upon cooling, the HPC gel, however, reverts to its original solution state, with virtually no change in the flow properties. Since the hydroxymethyl group is more hydrophilic than the methyl group, HPMC is more readily hydrated than MC. The hydration rate of HPMC increases with an increase in the hydroxypropyl content[48b]. The gelation temperature of MC is 50-55°C, whereas that of HPMC ranges between 58-90°C, depending on the hydroxypropyl and methoxyl contents[48a]. At the gelation temperature, both MC and HPMC form structured gels which are susceptible to shear thinning. Like HPC, both revert to their original solution state upon cooling. NaCMC remains soluble in cold and hot water[52].

All of these water soluble polymers (MC, HEC, HPC, HPMC, and NaCMC) have a tendency to agglomerate on wetting with water. Except NaCMC, all the other polymers can be best dissolved, without agglomerating, by adding the powder to the well-agitated hot water, followed by dilution with cold water (room temperature or lower). The dissolution of NaCMC in water is not critically dependent on temperature, and the solution can be prepared by sifting the powder into the vortexed of vigorously stirred water at room temperature. The (aqueous) solution viscosity of MC, HPMC, HEC, HPC, and NaCMC increases with an increase in concentration and molecular weight. It also changes with temperature, decreasing when warmed (below gelation temperature), and increasing when cooled. An increase in the temperature causes weakening of polymer-water interactions, and consequently, a decrease in the viscosity. At gelation temperature, a strong intramolecular hydrogen bonding occurs, causing desolvation, and precipitation of the polymer. Aqueous solutions containing higher concentrations or higher molecular weight grades of these polymers are generally non-Newtonian, that is, they exhibit pseudoplastic flow. Aqueous solutions of HEC and NaCMC generally show thixotropic properties, whereas solutions of MC, HPMC, and HPC exhibit little or no

thixotropic flow. The solutions of MC, HEC, HPC, and HPMC, owing to their non-ionic nature, are tolerant to pH changes and low concentrations of salts. However, above a certain concentration, salts compete for the available water, causing precipitation of the polymer from solution. CMC remains in solution in the presence of monovalent ions. In the presence of low concentrations of bivalent ions, the solution turns hazy in appearance, whereas the addition of trivalent ions causes precipitation of CMC from its solution. NaCMC solutions are most stable between pH 7-9. Below pH 4, the insoluble acid form of CMC predominates[52]. The aqueous solutions of all of these polymers are susceptible to microbial attack, and thus should be stored in the presence of an appropriate preservative.

NaCMC[52] and HEC[50] are insoluble in organic solvents, but dissolve in certain mixtures of water and water miscible organic solvents (e.g., alcohol and acetone). The solubility of MC and HPMC products in organic solvents varies, depending on the degrees of substitution. The best solvent systems recommended for most HPMC products are binary systems comprising methylene chloride (or chloroform) and alcohol. The solublizing power of the mixed system improves as the molecular weight of the alcohol decreases[48]. HPC has excellent solubility in polar organic solvents (methanol, ethanol, acetic acid, chloroform, cyclohexanone, dioxane, propylene glycol, dimethyl sulfoxide, dimethyl acetamide, tetrahydrofuran, binary solvent mixtures such as acetone-water (9:1) and benzene-methanol (1:1), etc.)[51].

EC is insoluble in water, but dissolves in a wide variety of organic solvents (e.g., esters, aromatic hydrocarbons, alcohols, chlorinated solvents). The solution viscosity increases with an increase in molecular weight and concentration. Concentrated solutions of EC are usually prepared in binary solvent systems consisting of appropriate ratios of an aromatic hydrocarbon solvent (e.g., toluene) and ethyl alcohol. The hardness and softening temperature of EC films first decreases and then increases with an increase in the ethoxyl content; the minimum values are at about 48.5% ethoxyl substitution[61].

MC, EC, HEC, HPC, HPMC, and NaCMC are all available in several viscosity (molecular weight) grades. The MC products, all meeting the USP specifications of 27.0-31% methoxyl content[47a], are marketed as Methocel A by Dow[48]. The EC is available in three types of ethoxyl substitution from Hercules Inc. (Grade N: 48.0-49.5%; Grade K: 46.1-47.2%; Grade T: 49.6% min.)[49a] and Dow Chemical Co. (Trade name: Ethocel®, Grade S: 48.0-49.5%; Grade M: 45.0-47.0%; Grade HE: 49.5-52.0%)[49b]. EC is also available in aqueous colloidal dispersion forms under the trade names Aquacoat®[53] and Surelease®[54], respectively. The Aquacoat® dispersion has a 28-32% solid content consisting of 24.5-29.5% ethylcellulose, 0.9-1.7% of sodium lauryl sulfate, and 1.7-3.3% of cetyl alcohol. Some effective plasticizers that can be used with Aquacoat® are dibutyl sebacate, diethyl phthalate, triethyl citrate (Citroflex-2), tributyl citrate (Citroflex-4), acetyl tributyl citrate (Citroflex-A4), and acetylated monoglyceride (Myvacet 9-40). Surelease® is marketed as a 25% solid (ethylcellulose, oleic acid, and fumed silica) dispersion in an ammonical water. Both Aquacoat® and Surelease® are used in coating and granulating applications and in taste masking processes. Compared to organic solvent based applications of EC, both Aquacoat® and Surelease® offer several advantages: i) these, owing to their totally aqueous in nature, pose no threat of toxicity in handling, and no organic solvent recovery system is required, during their applications; ii) the high solid content and the low viscosity of these dispersions make their use much easier in their applications; and iii) the high solid content and the large surface area of the particles significantly reduce the coating drying time (with evaporation of water, the boundaries of the particles come in contact and coalesce readily).

The HEC, HPC, and NaCMC products are commercially available from Aqualon™ under the trade names Natrosol®, Klucel®, and Cellulose Gum, respectively. HPC is also available from Dow Chemical Co. The hydroxypropyl content in the Aqualon™ HPC ranges between 66.0-74.3% percent[51a], whereas the Dow HPC contains 60-70% hydroxypropyl content[51b]. Of the four different types of HEC products available (Natrosol® 150, 180, 250, and 300), only Natrosol® 250 is currently used in

pharmaceutical applications. This product is 51.0-58.9% substituted, corresponding to the MS values of 2.2-2.8. The CMC is available both as a sodium salt and as a calcium salt. The NaCMC types 7 and 9 contain 7.0-8.9% and 8.1-9.2% sodium content, respectively, and thus meet the USP specification which requires the sodium content to be not less than 6.5% and not more than 9.5% in the product [47f]. NaCMC type 12 corresponds to the NF grade. The sodium content in this product ranges between 10.5-12.0% [47f]. A crossed-linked form of NaCMC, marketed as Ac-Di-Sol by FMC, is listed in the USP/NF as croscarmellose sodium, Type A [47h], and is used as a dissolution aid and disintegrant in tablets and capsules. Ac-Di-Sol shows dissolution/disintegration properties independent of tablet hardness, and is highly effective in wet granulation and direct compression products.

HPMC is sold under the trade name Methocel by Dow Chemicals. The four different types of products available are E, F, J, and K [48]. These correspond to the USP types 2910, 2906, 1828, and 2208, respectively [47d].

Numerous commercial applications of cellulose ethers are known. EC is widely used for solvent granulation of water-sensitive drugs, in tablet coatings, in microencapsulation, in taste masking processes, and as a binder in dry compression granulation or direct compression [61]. MC, HEC, HPC, HPMC, and NaCMC are all useful as thickening agents, rheology or flow control agents, protective colloidal agents, emulsion stabilizers, and suspending agents in oral and topical liquid solution/suspension formulations, and as film-forming agents in tablet coatings. The low-viscosity grades of MC (Methocel A 15LV) and HPMC, in low concentrations (2-6%), are useful as tablet binders, whereas the high viscosity grades ($\geq$ 4,000 cps; e.g., Methocel A4M, E4M, F4M, K4M, and K15M) are used in preparing liquid formulations (e.g., creams, lotions, gels, ointments, and suspensions) [48c]. The low viscosity grades Methocel E products are used in tablet coatings. The Methocel K products, owing to their reduced methoxyl content, have the fastest hydration rates, and therefore, are suitable for use in preparing controlled-release matrix tablets [48]. The HPC is thermoplastic, and thus can be extruded or injection molded at elevated temperatures [51].

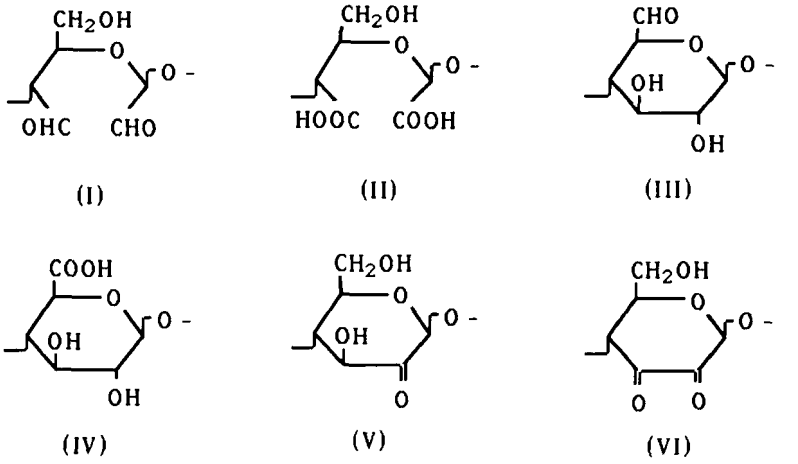


FIGURE 8

Possible Oxidized Anhydroglucose Units[55]

OXYCELLULOSES OR OXIDIZED CELLULOSES. These are prepared by treating cellulose with an oxidizing agent, such as gaseous oxygen[55], hydrogen peroxide[55], chlorine dioxide[55], nitrogen dioxide and/or dinitrogen tetraoxide[55], persulfate[56], dichromate-sulfuric acid[57], nitrous acid[58], nitric acid-nitrites[59,60], nitric acid-sulfuric acid-nitrites, nitrous acid and/or nitrogen monooxide[61], periodic acid-sulfuric acid[62], and alkali or alkaline earth metal hypohalites[55,63] or periodates[55]. Most oxidants are unspecific in their mode of attack, and different types of oxidation may occur simultaneously. Also, the oxidation of cellulose is always accompanied by varying degree of scission of the glycosidic bonds. Depending on the oxidant and the reaction conditions (e.g., temperature, pH, and concentrations of reagents) used, oxidized cellulose products may contain one or more of the following oxidized anhydroglucose units in the structure (Figure 8)[55].

The various applications of oxidized celluloses in cosmetic, pharmaceutical, medical and related areas include their use as: 1) coating materials for ferric and aluminum salt granules in the

formulation of microencapsulated astringent hemostatic agents[64]; 2) bodying agents in the preparation of cosmetic and pharmaceutical preparations[63,65]; 3) biocompatible antihemorrhegic absorbable materials for wounds and to stop bleeding during surgery[58,59,66]; 4) biological surgical threads; 5) fibrin formation-accelerating agents[67]; 6) enzyme carriers[66]; 7) kidney dialyzer membranes[66]; 8) deodorants for absorbent pads (e.g., dressing, diapers and catamenials)[57]; 9) sorbent to remove extra corporeal urea[66]; 10) drug carriers[66]; and 10) biocompatible mold release agents or donning powders and medical lubricants for surgical gloves and the like[68].

In the USP[69], two types of oxidized cellulose products are described. These are: oxidized cellulose and oxidized regenerated cellulose. The carboxylic content in the former is described not be less than 16.0% and not more than 24%, whereas in the latter it should lie between 18% to 24%. Oxidized cellulose products, conforming to USP specifications, are commercially available in the form of gauge, cotton, and powder from Eastman Chemical Co. These are reported to contain oxidized anhydroglucose unit IV (Figure 8)[66].

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